ORIGINAL ARTICLES.

THE THERAPEUTIC USE OF TUBERCULIN COMBINED WITH SANITARIUM TREATMENT OF TUBERCULOSIS.[1]

By E. L. Trudeau, M.D.,

DIRECTOR OF THE ADIRONDACK COTTAGE SANITARIUM, SARANAC LAKE, NEW YORK; PRESIDENT OF THE AMERICAN ASSOCIATION FOR THE STUDY AND PREVENTION OF TUBERCULOSIS.

The wild enthusiasm which greeted Koch's announcement in 1890 of his discovery of tuberculin and his claims for its diagnostic and therapeutic possibilities was, as you know, very soon followed by bitter denunciations of the proposed method of treatment, and even of the distinguished scientist himself. Tuberculin was soon abandoned, and for a long time was considered as so dangerous that its use was looked upon as akin to malpractice. A few physicians, however, both here and abroad, continued the study of its careful application to cases of pulmonary tuberculosis, and of late more frequent publications on this subject point to renewed interest in the employment of some sort of vaccine as an immunizing agent in this disease.

So general and bitter was the condemnation of tuberculin that between 1891 and 1900 it was with the utmost difficulty that I could persuade a few patients at the Sanitarium each year to take the treatment while in the institution. As I have, however, used tuberculin injections continuously, though at times in a limited number of cases only, at the Sanitarium ever since 1890, I have thought that a summary of the impressions I have gained from my experience might prove of interest. Dr. Lawrason Brown has already published a detailed report of the cases treated at the Adirondack Cottage Sanitarium up to 1903. I shall not attempt to review the extensive literature of the subject, to discuss lengthy statistics bearing on the comparative results, or to go into a detailed history of cases, but will merely confine myself, as far as possible, to my own experiences, and briefly state my impressions of this method of treatment.

As a diagnostic agent, the tuberculin test has been used at the Sanitarium occasionally for the past fifteen years. So far as its danger is concerned, my observation has been that when given according to the well-recognized rules which alone make its administration justifiable I have never known any ill effects follow the test beyond occasionally a somewhat severe or prolonged reaction, except possibly in three cases, which were somewhat unpleasant experiences. One occurred in the practice of another physician, and two were at the Sanitarium. In the first case there was constitutional impairment, without any marked physical signs, and a test injection of old tuberculin resulted in a moderate reaction, which subsided, but was soon followed by an aggravation of all the symptoms, and I believe the patient ultimately did badly. The other two cases were at the Sanitarium. In one case, a slight hemorrhage followed the first reaction two weeks after its subsidence, but there was no other ill effect. In the other, after four days of normal temperature following the first reaction, blood-spitting occurred, and an exacerbation of all the symptoms, with marked fever, followed and continued for some time. Whether these occurrences were merely coincidences, or were due directly or indirectly to the tuberculin, it is difficult to be certain.

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[1] Read at the meeting of the National Association for the Study and Prevention of Tuberculosis, Washington, D. C., May 17 and 18, 1906.

Picket, who recently injected 929 patients, in order to confirm a diagnosis of pulmonary tuberculosis when the bacillus was absent, saw quite prolonged disturbance of the patient's condition follow in three cases, while in twenty the reactions were "more violent than desirable." At the Sanitarium the test has been of great value in helping to reach a conclusion as to the absence or presence of tuberculosis, especially in closed tuberculosis, or when the tuberculous nature of a pulmonary lesion was in doubt; a conclusion which, in the great majority of cases, has proved to be correct and of inestimable value to the patient.

The tuberculin test should never be resorted to until the physician has failed to reach a conclusion after a careful application of the clinical methods of diagnosis. As our skill in the detection of closed tuberculosis increases, it may be necessary to use the test only in exceptional cases, as the reactions at best are sometimes an unpleasant experience for the patient. On the other hand, the more we realize how really curable closed tuberculosis is the more valuable becomes a method which reveals its presence when all other clinical means fail.

I have persisted in the study of tuberculin treatment at the Sanitarium, not on account of any immediate brilliant results noticed in its application, although I saw enough of its effects to encourage me to persevere in its use; but principally, in spite of the popular clamor against it, because it is based on a certain degree of success demonstrable in animals by the experimental method, and because the production of artificial immunity by the specific poison of a disease is the line along which success has already been attained, and is being attained, in other infectious diseases.

The experimental evidence on which tuberculin treatment is based is not as complete or satisfactory as one would wish. Koch gave no details of the method by which he attempted to immunize and cure guinea-pigs with old tuberculin, T. R., or Bacillen Emulsion, but merely states that they can be rendered resistant to subsequent inoculations, and that when treated by these products, their lesions show marked evidence of fibrosis. His associates published details of experiments, but the results, although encouraging, did not show complete cure or immunity. Other observers have reported a varying degree of success in the immunization of small animals, and in their treatment by bacillary products. Broden,[1] perhaps, gives one of the most detailed descriptions of the good results which he obtained in dogs injected with the filtrate of liquid cultures, both before and after intraperitoneal inoculation, and demonstrates the curative influence of tuberculin as shown by a comparative microscopic study of the lesions of the treated and the untreated animals, as well as by the survival of the former and the death of the latter. Pathological observations bearing on the microscopic appearances of the lesions of patients who have been treated successfully with tuberculin, and have died of other causes, would be of great value at present.

The most convincing evidence of the favorable results of tuberculin that my own experimental work has shown me, I obtained and published as early as 1892. By treating tuberculous iritis in the rabbit's eye by subcutaneous injections of the unheated filtrate of bouillon cultures of the tubercle bacillus, a retrogression of the lesion and an apparent healing gradually took place, which, however, ultimately relapsed somewhat, though very slowly. I have found that guinea-pigs and rabbits previously injected with dead tubercle bacilli live on an average somewhat longer than control animals when subsequently inoculated. The beneficial influence of treatment of small animals with various products of the tubercle bacillus, however, is demonstrated, not by the cure of a progressive generalized tuberculosis in them, for this does not occur; but by the evident tendency to healing shown in localized tuberculosis, and in the more chronic course of the disease in the treated as compared with the untreated animals.

The immunity obtained by non-living products of the tubercle bacillus, however, is only relative, and is not to be compared to that which I have been able to produce by preventive inoculations of living attenuated cultures. Behring's experiments of cattle immunization thus far published show the same thing, namely, that he obtained no solid immunity in cows with various *non-living* tuberculous products, but that he achieved success and produced a solid immunity by previous inoculations of living human cultures. All these experiments establish for tuberculosis, by unquestionable evidence, the principle of artificial immunization, hitherto looked upon as impossible of achievement.

Animal experiments, therefore, on which tuberculin treatment in man is based, show that tuberculin immunity is not identical with immunity to tuberculosis, for it does not protect animals absolutely against inoculation tuberculosis, nor materially retard the course of generalized tuberculosis. It would seem that contact between the living bacillus, or the product of the living bacillus, and the cell, is necessary to the production of a solid and lasting immunity, for up to the present this immunity to tuberculosis or to other bacterial diseases has been accomplished in animals only by protective inoculations of a living germ. Behring, however, in his recent announcement claims to have discovered a successful method of immunization for cattle without the use of living bacilli.

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[1] Recherches sur l'histogenese du Tubercle et l'action curative de la Tuberculine. Archiv. de Médecine Experimentale, January, 1899.

Nevertheless, tuberculin immunization, even in the most susceptible animals, undoubtedly prolongs life somewhat, retards the development of the disease in its earlier stages, and produces changes in the lesions which demonstrate an attempt at healing, and this, in localized tuberculosis, may be equivalent to a more or less complete cure. The limitations of tuberculin in the treatment of experimental tuberculosis in animals should, therefore, be borne in mind in judging the results of tuberculin treatment in human beings. Why should we expect it to do more for man than it can accomplish in animals?

To what extent, if any, does tuberculin immunization induced in man favorably influence the course of human tuberculosis? From the renewed interest in this form of treatment it seems that the claims of this method are soon to be thoroughly and dispassionately settled.

Most of the proposed tuberculins have been tested at the Sanitarium. The first used was Koch's original tuberculin. Later, after the publication of Hunter's work in 1891, I made his Modification B., myself, from the filtrate of liquid cultures. The albumoses contained in the unheated culture medium, having been precipitated with ammonium sulphate, were taken up in distilled water and dialysed, Hunter claiming more local and less general reaction from this product. This preparation was used at the Sanitarium for a time. In 1898, Buchner's Tuberculo-plasmin, and in 1900, Landmann's Tuberculol, were both tried, as well as Koch's T. R., and since 1901, Koch's Bacillen Emulsion has been principally used; but Koch's three tuberculins have been most generally employed.

The use of these preparations gave rise to symptoms which were nearly identical, and are the well-known ones of tuberculin reaction. It has been impossible to reach any conclusion as to the relative therapeutic value of these different preparations. Koch's T. R. and Bacillen Emulsion seem to be more uncertain in their action, and to produce more frequently strong and unexpected reactions. This is a serious objection to their use, as occasionally unexpected and pronounced reactions occur, even if the dose is increased with the utmost caution. The reason for this undoubtedly, to a great extent at least, lies in the fact that they are mostly emulsions and not solutions; that absorption of such a suspension is much more difficult and uncertain than that of a readily soluble toxin; and that unless great care is exercised in thoroughly shaking the bottles, and in drawing from the centre of the liquid rather than the top or bottom, the dilutions made will contain very varying amounts of the suspended but undissolved bacterial substance.

Reasoning from analogy and from what we know of artificial immunization in other bacterial diseases, tuberculins in the preparation of which no heat has been applied are likely to be the most efficient. Koch's Bacillen Emulsion, and the filtrate of ripe cultures as used by Denys, meet this requirement. The first contains all the toxins and endotoxins to be found in the bodies of crushed tuberle bacilli; the second, the toxins and any other substances which may be produced by the growth of the bacilli, or dissolved from their disintegrating bodies in a liquid medium, and both are entirely unaltered by heat.

It is possible that the chemical researches of de Schweinitz, Levene, Behring, Ruppel, and others, exhaustive as they have been, may be carried still further, and that organic chemistry may yet produce a more efficient tuberculin by the elimination of certain substances which are injurious, and the retention of others which are immunizing. But Koch's long and careful work in this direction is suggestive, for after prolonged investigations which resulted in his T. R. tuberculin, he has more recently put forth his Bacillen Emulsion, which is merely a suspension of crushed tubercle bacilli, and contains entire and unaltered all the toxins contained in the bodies of the bacilli. Behring's announcement, on the other hand, is full of encouragement. His T. C. is a toxin which differs from Koch's T. R. principally in its freedom from the waxy elements contained in the bodies of the bacilli, and it is possible it may prove to be a more efficient tuberculin than any we now possess. From what we may infer from Behring's guarded and enigmatical utterance, he has gone even further, and it would seem that he has succeeded in transforming by contact with the living cell his T. C., which is a toxin, into his "Tuberculase," which is an immunizing and curative substance capable of immediate absorption by the cells of susceptible animals and man, and thus producing the desired immunity. Dr. Theobald Smith, as a result of his recent studies on animals, suggests virulent uncrushed tubercle bacilli, killed by moderate heat, as the best vaccine to be tried in attempts at immunizing human beings.

With a few exceptions, in which, soon after Koch's discovery, tuberculin was given as a last resort to far advanced patients who begged to be treated, the patients selected for treatment at the Sanitorium have belonged to the incipient and advanced class, who were mostly apyretic, or whose temperature at irregular intervals reached only from 99.5° to 100°, and whose general nutrition was good. The acute types, or those suffering from marked febrile remission or hectic fever, were excluded. Patients running a continuous temperature, even if not above 100°, with little to be heard in the lungs, but with rapid pulse, emaciation, debility, and cachexia, pointing to scattered miliary tuberculosis, were also excluded. Elsassar, Denys, and others advocate the use of tuberculin injections even in acute febrile cases, but I have had no experience with such cases.

For a long time the tendency was to choose as favorable cases as possible, from both the incipient and advanced classes, for treatment; but little by little less favorable cases were selected, and during later years those whose condition seemed to be at a standstill, and to have but little chance of arresting their disease by the hygienic and open-air method alone, have been frequently treated. It cannot be denied, however, that the desire to select, from whatever class, patients whose nutrition was good, prevailed to a greater or less extent, and must have somewhat influenced the results.

The first impression which the physician receives who begins to make use of tuberculin is a most profound respect for the tremendous potency of this toxin. A toxic substance which, in so infinitesimal a dose as the one five-thousandth of a milligram of the solid substance contained in Koch's Bacillen Emulsion, may produce typical and marked constitutional disturbance in the tuberculous individual, is certainly not to be used heedlessly, and is potent for evil if carelessly administered. I would not urge any physician who prizes his peace of mind to embark on the treatment of tuberculosis by this method unless he is prepared to begin with minute doses and increase with the utmost caution. He will also soon be made to feel the deep-rooted prejudice which exists, both in the profession and laity, against tuberculin treatment, and he must be prepared to meet criticism and blame for all the exacerbations and complications which naturally develop in the course of the disease, and which are invariably attributed not to the disease but to the treatment; while coincidences will occur occasionally which make his position indefensible, and which he must be prepared to face as best he can. I have seen tuberculous meningitis, hæmoptysis, and uncontrollable pyrexia, all ending fatally, occur in patients who were about to take tuberculin, but for some reason or other did not take it.

The method of administration is of the greatest importance, and has varied as time passed. At first little attempt was made to avoid reactions, which were advised by Koch, and which he still seems to consider as necessary to success in this form of immunization, for in his last paper on Bacillen Emulsion he says: "One increases the dose very rapidly in order to obtain very pronounced reactions, with elevations of temperatures of 1.5° to 2° C. As soon as a strong enough reaction is obtained, the intervals must be lengthened to from six to eight days or more."

From my own experience with tuberculin I have formed the impression not only that fever reactions are not necessary to obtain good results, but that although occasional moderate reactions are unavoidable and apparently do no harm, every effort should be made to avoid them. If frequent and violent, they have a bad effect on the patient's general condition, and are by no means free from danger, as was shown during the early history of tuberculin treatment, the danger being the production of continuous fever, cachexia, and increased activity in the disease.

If we abandon the view that fever reactions are necessary to obtain results, and look upon them as the result of overstimulation; if we accept as a working theory that any curative influence of tuberculin is due not only to a local reaction of the lesion but also to a stimulation of the body cells by the injected toxins—a stimulation which results in the production of some sort of anti-body by these cells, as well as possibly an increased activity of the phagocytes—the best method of treatment would undoubtedly be to continue this stimulation by minute and very gradually increased doses for as long a period of time as possible. Whatever reactions unavoidably occur are only to be considered as indicating that the limit of the patient's capacity for responding, by the formation of antitoxic or antibacterial substances, to the stimulus of the injections has been exceeded.

We must divest our minds of the impression that because small doses produce no immediate apparent effect they are, therefore, ineffectual, for we have ample evidence to the contrary. A minute amount of tuberculin, which produces no rise of temperature when injected in rabbits with tuberculous iritis, nevertheless is capable of bringing about a very appreciable local reaction and leukocytosis. The same occurs in tuberculous nodes and lupus, and the work of Wright and Douglas proves that minute doses, and a very gradual increase, are met by a very appreciable and easily demonstrable response of the defensive resources of the living organism.

The best method has seemed to me to begin with very minute doses—1/10,000 or even 1/20,000 of a milligram of solid substance Koch's Bacillen Emulsion, or a 1/100 of a milligram of old tuberculin—and increase so gradually and at such intervals as to carry the patient to full doses with as little disturbance as possible; and by taking sufficient time, most patients can be taken through the entire treatment with but occasional and moderate reactions. At the slightest evidence of intolerance, as manifested not only by the patient's temperature, but by his symptoms, by marked irritation at the site of injection, or depreciation of his general condition, the intervals between the injections should be lengthened and the dose diminished for a time. Care should be taken never to inject after a reaction until all effects of the previous reaction, both on the patient's temperature and general condition, have entirely passed away. I have also formed the impression that the treatment should be extended over as long a time as is needed to avoid reactions, no matter how long that may be, and that time is an important element in obtaining the best results. Six months of treatment is almost always necessary, and a year or more would be better in many cases.

The patient, while taking the injections, should show no depression of general health, and should have no fever above his usual temperature range, except it be occasionally for the forty-eight hours following an increase of dose; if this occurs the treatment should be discontinued, and only resumed when he has recovered his normal condition. If full doses, that is, 1 c.c. of old tuberculin, or 5 milligrams of solid substance Bacillen Emulsion, can be reached without violent reactions and without depreciation of the general health, *but not otherwise,* the injections should continue until one full dose has been given; but the intervals should be lengthened gradually as the higher doses are reached, and extended to two weeks between the last two or three injections. The physician must, of course, individualize, and be guided throughout the treatment, and in his judgment *as to the dosage to which it is to be carried,* entirely by its effect on the patient; and on his watchfulness and skill will greatly depend the safety of the patient and the degree of success attained.

I quite agree with Denys that the principal faults in treatment—faults which may lead to failure, and even seriously endanger the patient's chance of recovery—are:

Beginning the treatment with too large amounts; raising the dose too rapidly or at too short intervals; injecting again before all effects of a reaction, both constitutional and local, have passed away; increasing the dose after a reaction has occurred; neglecting to consider malaise, headache, loss of appetite, and increased cough, as evidences that the limit of the patient's tolerance has been reached, and calls for an interval of rest and a reduction of the dose. The physician who disregards as of no importance an increase of a minute fraction of a milligram of tuberculin, or a rise of a few tenths of a degree of temperature, will meet with disappointment and disaster in the application of tuberculin treatment. I have become convinced that any danger there may be of aggravating the patient's condition by tuberculin treatment lies principally, if not wholly, in its faulty or reckless administration.

Tuberculin immunity does not last indefinitely, and it may be well for the patient to take another course of treatment in four to six months if any symptoms should reappear; but with a very few exceptions the patients at the Sanitarium have taken but one course of injections.

The serum agglutination method, as proposed by Koch, has not been found reliable either as a guide to dosage or as an indication to the degree of immunization produced by tuberculin.

The most interesting work of Wright and Douglas on the production of opsonins in the blood, the presence of a positive and negative phase in artificial immunization, and finally the application of the opsonic index as an accurate guide in regulating the doses of vaccine and intervals between injections, is a brilliant contribution to our knowledge of the mechanism of artificial immunization, and a striking attempt at the practical application of exact laboratory methods to the treatment of disease. It is to be regretted, however, that even if the deductions Dr. Wright draws as to the necessity of being guided by the rise and fall of the opsonic index, and even if the accuracy of his method of determining it should be confirmed, the degree of skill required in carrying out such delicate technique and the time and work necessary in the determination of the opsonic index, make it generally impractical of application to the treatment of disease in a large number of patients. Besides, as Elsassar remarks in regard to the agglutination method, the patients object to periodical phlebotomies; the reactions are quite enough for them.

The immediate results of tuberculin treatment are not very striking, and up to the time of discharge (generally six months), when patients, treated and untreated, who were classified alike on admission, are compared, there is little difference to be noted in their condition, as the majority, especially in the incipient class, whether treated or not, show more or less marked improvement in symptoms and general condition. It is rather when studying the effect of the injections in patients somewhat more advanced in the disease that one notes occasionally unusually rapid and unexpected improvement, and that the preponderance of improvement seems to be in favor of the patients who have taken tuberculin.

The physical signs in tuberculin-treated cases may appear to grow worse, and rales develop where they were not heard at first, while the expectoration increases; but if no strong reactions have occurred this is not marked, and everything in the chest soon returns to its usual condition and the expectoration lessens if the doses are not pushed too rapidly. Even the disappearance of bacilli is often not much more marked in the treated than in the untreated incipient cases up to the time of discharge, but in advanced cases the comparison with similar untreated cases is in favor of the treated.

I nevertheless have formed the impression that the use of tuberculin brings about somewhat better results than can be obtained by sanitarium methods alone, even up to the time of discharge. The statistical evidence I have been able to gather, and which seems to confirm these impressions, was made for the Sanitarium records at my request by Mr. E. S. Pope, an expert mathematician, to whom my acknowledgments are due; and I present the evidence of his exhaustive study in as condensed form as possible.

The influence of tuberculin injections on the disappearance of bacilli from the expectoration, when the entire number of treated and untreated patients at the Sanitarium is considered, is as follows:

Of those who had bacilli in the incipient class, 64 per cent. of the untreated and 67 per cent. of the treated lost them; of those classified as advanced on admission, 44 per cent. of the treated lost them, and 24 per cent. of the untreated.

In regard to the results at discharge, Mr. Pope writes: In some years there have been few, and in other years many tuberculin cases. The standards of classification have varied from time to time. Now if there were a large number of treated cases in a year of low standard, the tendency would be to make the total results for tuberculin unduly good. If these conditions were reversed, the opposite result would be obtained. By reducing (or increasing) the numbers of treated and untreated cases to one hundred in each class, in each year, this difficulty is avoided. The correct way to do this is not to select the cases, but to multiply or divide the actual numbers in each class for each year so as to make them equal to one hundred. This applies to the following table:

Comparison of 185 *Patients Treated and* 864 *Untreated.* There have been excluded all who stayed less than ninety days, and all who did not have tubercle bacilli on admission.

For the reasons given above, the following percentages have been calculated on the basis of an equal number of treated and untreated patients in each year.

The results at the time of discharge were as follows:

	Incipient.			Advanced.		
	Apparently cured.	Disease arrested.	Active.	Apparently cured.	Disease arrested.	Active.
Treated . . .	56 p. c.	34 p. c.	10 p. c.	27 p. c.	55 p. c.	18 p. c.
Untreated . .	50 p. c.	38 p. c.	11 p. c.	6 p. c.	51 p. c.	43 p. c.

In considering these figures we are at once struck with the fact that the advanced cases, both so far as the loss of bacilli and the condition at discharge are concerned, seem to derive proportionately much more benefit from the treatment than the incipient cases. I will refer to this later. You all know how unsatisfactory and unconvincing conclusions based solely on statistics relating to sputum examinations and classification of results can be. The uncertainties of sputum examinations, unless several examinations extending over considerable time are made, and the personal equation of the physician cannot be excluded as influencing the classification of a patient at discharge, and are among the most obvious and misleading sources of error in such statistics.

The study of the post-discharge mortality, however, would seem to promise much more satisfactory and conclusive evidence. Through carelessness we may all fail to find bacilli though they be present; and we may all differ as to whether a patient at discharge is "apparently cured" or the disease "arrested;" but there can be no doubt as to whether the patient be living or dead. Besides, the object of sanitarium treatment is not the condition of the patient at discharge but the prolongation of his life, and time must ever be the crucial test of any treatment. Mr. Pope has condensed for me his canvass of the post-discharge mortality, which bears on 135 treated and 690 untreated patients discharged in the past fifteen years from the institution.

Comparison of 135 *Patients Treated and* 690 *Untreated.* Equal numbers of treated and untreated patients in each year are considered; all patients who stayed less than three months, all who left the Sanitarium less than one year ago, and all untraced patients have been excluded.

	Incipient.		Advanced.	
	Living.	Dead.	Living.	Dead.
Tuberculin treated	79 p. c.	21 p. c.	61 p. c.	39 p. c.
Untreated	63 p. c.	37 p. c.	36 p. c.	64 p. c.

From these figures we gather that 18 per cent. more of treated incipient cases are living than of untreated, while 25 per cent. more of advanced cases who received tuberculin are living than of those who did not. The value of such comparative statistics, however, depends entirely on two things: the accuracy of the figures, and the explanation of the results they represent. As to the accuracy of the figures I have little or no doubt, but I regret that I am by no means so certain of their exact value as demonstrating the curative influence of tuberculin. The question is, Are the favorable results which these figures seem to indicate due solely to tuberculin treatment or to other factors?

The only sources of error with which I am acquainted are the influence of the selection of cases, and the fact that the treated remained often much longer in the institution, in order to complete their treatment, than the untreated.

It is impossible to estimate how much the selection of cases has influenced the results, and the more favorable comparative results obtained in the advanced class may be interpreted in two ways, and does not help us much in reaching a correct conclusion. Any specific curative influence of tuberculin would be shown more markedly by prolongation of life in the advanced class, in which the disease was tending toward a fatal termination, than in the incipient class, in which the disease in the majority of cases inclined to arrest and cure without the aid of any specific treatment. On the other hand, selection of cases would have more influence on the results in the advanced than in the incipient class, because the advanced class is much more comprehensive than the incipient, and there is often as much difference between favorable advanced and unfavorable advanced cases as between incipient and advanced.

Having stated the facts, I must, therefore, leave the interpretation of the figures to the individual judgment of those who may be interested in them. Many years ago, in spite of the general denunciation of tuberculin, and long before I knew anything about the statistical evidence, I had formed the opinion that tuberculin, when carefully administered, had within certain limits a favorable influence on the course of the disease, and that the results of sanitarium treatment could be improved and made more permanent in many cases by its application. As years have passed I have seen no reason to change this opinion, which the figures I have just quoted, however they may be interpreted, do not at any rate tend to contradict.

REVIEW OF THE WORK UPON THE OPSONIC INDEX (WRIGHT AND DOUGLAS) IN TUBERCULOSIS.[1]

By Nathaniel Bowditch Potter, M.D.,

Norman E. Ditman, M.D.,

and

Ernest B. Bradley, M.D.,

of New York.

Historical. Ehrlich's theory of immunity developed the conception that before a bacterial intoxication can take place a definite chemical union must exist between the cells of the affected individual and the toxins of the invading microbe. Wright named the various toxins "tropins," because they are substances which turn toward a cell. He calls the toxin of tetanus a "neurotropin," because it combines with the nerve cells. Such a union between tropins and cells calls forth a reaction upon the part of the infected individual to produce so-called "antitropins," which are protective substances. Many kinds of antitropins exist—antitoxins, agglutinins, precipitins, lysins, opsonins, etc. Wright believes that a sufficient amount of such substances within the body is responsible for the existence of natural immunity, and that their elaboration is capable of conferring an artificial immunity. The art of

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[1] Read in part by one of us at the meeting of the National Association for the Study and Prevention of Tuberculosis, Washington, D. C., June 17 and 18, 1906.